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EFFECT OF EXCIPIENTS ON THE STABILITY OF LEVOTHYROXINE SODIUM TABLETS

V. Das Gupta, C. Odom,* C. Bethea* and J. Plattenburg*

*University of Houston, 1441 Moursund St, Houston and *Ben Taub General Hospital, Houston, U.S.A.*

SUMMARY

Levothyroxine sodium tablets from two different manufacturers were analysed using the USP-NF method of analysis, a stability-indicating high pressure liquid chromatographic (HPLC) procedure. The results indicate that one particular manufacturer's 0·2-mg pink tablets contain some excipient(s) which act as a catalyst to hasten decomposition after extraction of levothyroxine for analysis. The same tablets from a different batch showed an additional long peak in the chromatogram, which indicated that the excipient(s) may have been changed. The same manufacturer has also used three different types of bottles/lids for the same product during the last year. Good manufacturing practice requires that new compatibilities/stability studies be conducted to assure the quality of the product. Ongoing stability studies are required by the Food and Drugs Administration (FDA). The use-life of 0·2-mg pink tablets of this manufacturer may be short.

Levothyroxine sodium is not a very stable compound (1, 2). In one study (1), levothyroxine sodium was reported to be very sensitive to irradiation, hydrolysis, oxidation and heat. In another study (2) conducted by the FDA, a number of commercially available dosage forms of levothyroxine sodium were found to be subpotent when assayed using the HPLC method. The FDA stated 'this fact indicated that the problems of low assays of marketed sodium levothyroxine are in all probability, attributable to sodium levothyroxine instability'. The FDA considers levothyroxine as an example of those drugs which have serious bioequivalence problems (3). A manufacturer of sodium levothyroxine tablets told us that their products decompose by approximately 1% per month. A medical representative of a reputed pharmaceutical company stated that some of the levothyroxine sodium tablets decompose by up to 40% in 30 days once the bottles are opened by the patients who usually receive up to 100 days' supply at a time. The reason given for the decomposition was the use of wrong excipient(s).

The purpose of these investigations was to determine the effect of excipient(s) on the stability of levothyroxine sodium tablets using the stability-indicating HPLC assay method of United States Pharmacopeia–National Formulary (USP–NF) (4).

Correspondence: Dr V. Das Gupta, University of Houston, 1441 Moursund St, Houston, TX 77030, U.S.A.

MATERIALS AND METHODS

Chemicals and reagents

All the chemicals and reagents were USP–NF or American Chemical Society (ACS) grade and used without further purification. Levothyroxine sodium powder was purchased from Aldrich Chemical Company and used as received. The hydroxyprogesterone caproate (the internal standard for HPLC assays) was generously supplied by E. R. Squibb & Sons, Princeton, NJ, U.S.A.

HPLC system

A Waters ALC 202 liquid chromatograph equipped with a multiple wavelength detector (Spectroflow 770, Applied Biosystems), a recorder (Omniscribe 5213-12, Houston Instruments), and an injector (Rheodyne Model 7125) were used. Microbondapak CN (30 cm × 3·9 mm i.d.) was the stationary phase and the mobile phase contained 35% (v/v) acetonitrile and 0·1% (v/v) phosphoric acid in water. The flow rate was 3 ml/min, the sensitivity was 0·1 (225 nm), the chart speed was 30·5 cm/h and the temperature was ambient.

Preparation of stock and standard solutions of levothyroxine sodium and hydroxyprogesterone caproate

The stock solution of levothyroxine sodium was prepared by dissolving 25·0 mg of the powder (on anhydrous basis) either in 0·01 N NaOH solution in 50% methanol in water (4) or in 0·01 N NaOH solution in 75% methanol (v/v) in water to make 50·0 ml. These solutions were prepared fresh daily. The stock solution of hydroxyprogesterone caproate was prepared by dissolving 50 mg of the powder in enough methanol to make 100·0 ml. This solution was prepared fresh every week. The most commonly used standard solution was prepared by mixing 2·0 ml of the stock solution of levothyroxine sodium with 4·5 ml of the stock solution of the internal standard and bringing it to volume (50·0 ml) either with 0·01 N NaOH solution in 50% methanol or in 75% methanol (see above) in water.

Assay sample of levothyroxine sodium from tablets

Either five 0·2-mg tablets or three 0·3-mg tablets were ground to a fine powder and the powder was mixed with 4·5 ml quantity of the stock solution of the internal standard. A 20·5-ml quantity of either 0·01 N NaOH solution in 50% methanol or in 75% methanol was added. The mixture was shaken intermittently for 5 min and filtered (Curtin Cat #263-798). The first 5 ml of the filtrate were rejected and then the clear filtrate was collected for assay.

Assay procedure

A 25-µl quantity of the assay sample was injected into the chromatograph using the conditions described. For comparison, the standard solution (containing identical concentrations of the drug and internal standard based on the label claim except for 0·3 mg tablets) was injected after the compound eluted.

Calculation

As preliminary investigations indicated that the ratio of peak heights (drug/internal standard) was directly related to the concentrations of the drug (range tested ± 50%

of the standard solution concentration), the results were calculated using a simple equation:

$$\frac{(R_{ph})a}{(R_{ph})s} \times 100 = \text{percentage of the label claim found.}$$

In the case of 0·3-mg tablets, the above results were divided by 0·9 because the assay sample contained only 90% of the drug relative to the standard solution. In the above equation, $(R_{ph})a$ is the ratio of the peak heights (drug/internal standard) of the assay and $(R_{ph})s$ that of the standard.

RESULTS AND DISCUSSION

Assay method

The HPLC method used is reported in the USP-NF (4). However, USP-NF does not recommend any internal standard. In our laboratory, there was a problem of reproducibility without the use of an internal standard. The internal standard developed (hydroxyprogesterone caproate) eluted after levothyroxine, which was necessary as the major products of decomposition (T_2 and T_3) of levothyroxine elute before the intact drug. With the use of an internal standard, the results were reproducible, accurate and precise with a percentage relative standard deviation of 1·5 based on five readings.

Results of analysis

For convenience, the tablets analysed were labelled as follows.

lot 1A—0·2 mg pink tablets of manufacturer A,
lot 2A—0·2 mg pink tablets of manufacturer A (different lot than 1A),
lot 3A—as above (different lot than 1A or 2A),
lot 4A—0·3 mg green tablets of manufacturer A,
lot 1B—0·2 mg pink tablets of manufacturer B.

Results with 0·01 N NaOH solution in 75% (v/v)

Using clear vials for the filtrate, the initial results for all the samples varied between about 96 and 99·5% and were therefore within the USP-NF limits (4). For the initial results, the sample was injected immediately after the filtration. The other times given were recorded based on the 0 min injection. When the samples were injected later, which is a common practice in any analytical laboratory, as single injection results are not considered accurate and precise, the results of lot 1B (0·2 mg pink tablets of manufacturer B) and lot 4A (0·3 mg green tablets of manufacturer A) were similar to the initial results, even after 120 min [Fig. 1(C–D)]. However, for lots 1A to 3A (0·2 mg pink tablets of manufacturer A) there was fast decomposition of levothyroxine [Figs 1(A–B) and 2(B–C)]. For example, on reinjecting the sample after 60 min, results were less than 90% of the initial value. The decomposition followed first-order kinetics (Fig. 3) with an estimated decomposition rate constant of 0·1 h^{-1}. In Fig. 3, the 0 min reading is off the straight line, presumably due to decomposition during the extraction procedure as required by the USP-NF (4). The extraction procedure requires occasional shaking during the 5 min prior to filtration. A similar decomposition process was found in all three lots (1A–3A) from manufacturer A but none in lots 4A (0·3 mg green tablets)

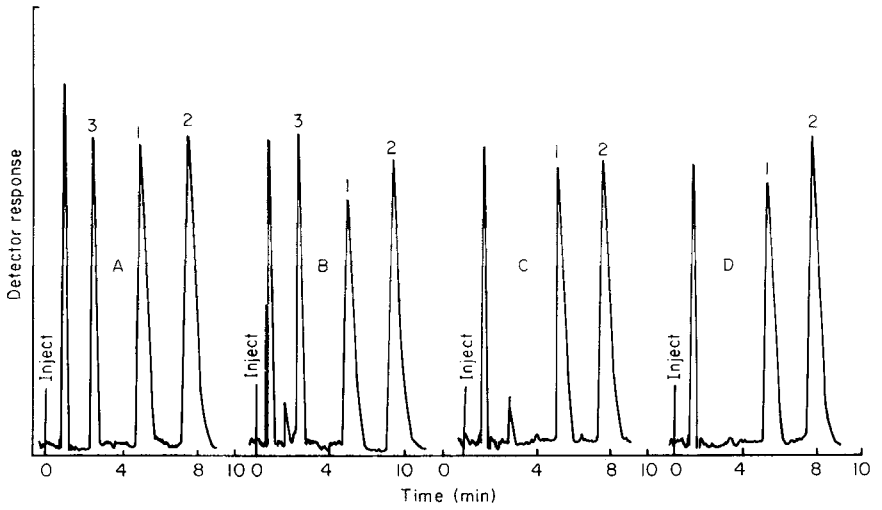

Fig. 1. Sample chromatograms. Peaks 1–3 are from levothyroxine, hydroxyprogesterone caproate (the internal standard) and an unidentified compound from 0·2-mg pink tablets (lot 3A), respectively. Chromatogram A is from a 0 min sample of lot 3A tablets; B from the same sample as A except after 60 min; C from a 120-min sample of lot 1B pink tablets; and D from a 120-min sample of 0·3-mg green tablets (lot 4A). For chromatographic conditions, see text. Seventy-five per cent aqueous methanol were used for extraction.

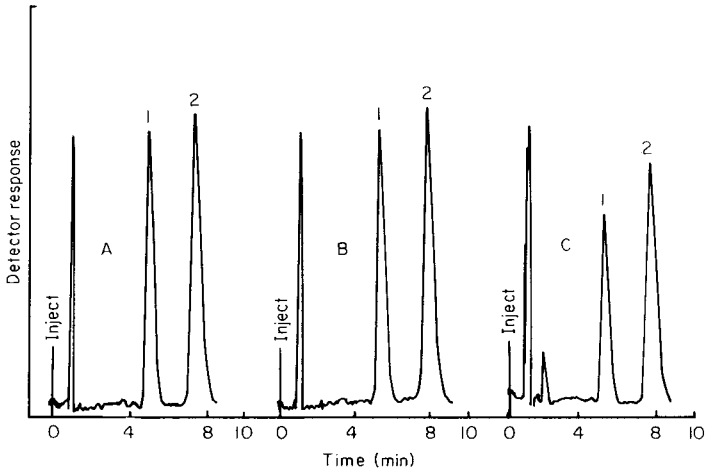

Fig. 2. Sample chromatograms. Peak 1–2 are from levothyroxine and hydroxyprogesterone caproate, respectively. Chromatogram A is from a standard solution; B from a 0 min sample of 0·2 mg pink tablets (lot 1A); and C the same as B except after 120 min. For chromatographic conditions, see text. Seventy-five per cent aqueous methanol were used for extraction.

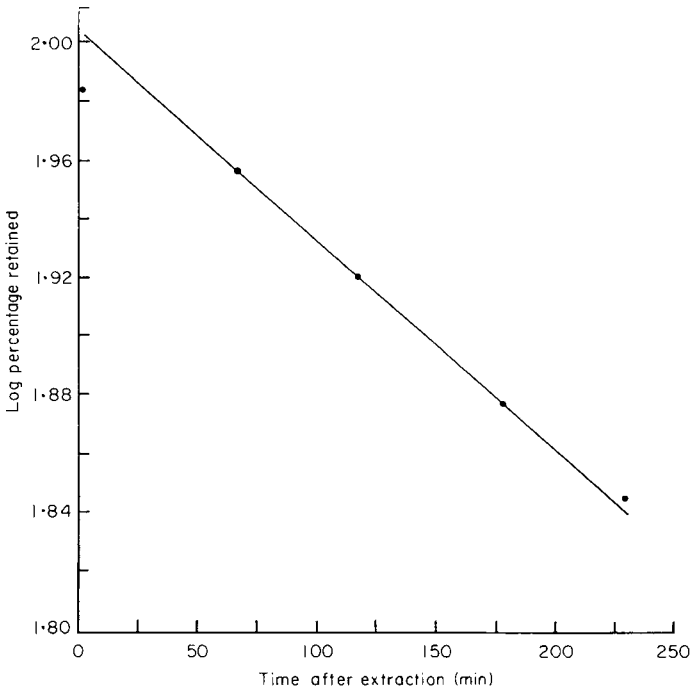

Fig. 3. A first-order plot of the log percentage retained versus time (min) after extraction of levothyroxine for 0·2-mg pink tablets (lot 1A).

and 1B. Furthermore, the chromatograms of lot 1A and 3A were different (Figs 2B and 1A, respectively). In lot 3A, there was an additional peak (peak 3, Fig. 1A) in the chromatogram. Apparently, manufacturer A may have changed the excipient(s) without conducting further stability studies as both lot 1A and 3A had the same inserts.

Effect of water on the decomposition constant

When 0·01 N NaOH solution in 50% aqueous methanol was used for extraction, the decomposition constant value for lot 1A–3A had approximately doubled (0·2 h^{-1}). The USP-NF procedure recommends 0·01 N NaOH solution in 50% aqueous methanol for extraction. With a k value of 0·2 h^{-1}, the loss in concentration of levothyroxine was about 18% when the same solution was reinjected after 60 min. The percentage loss in the standard solution, lot 4A and 1B samples were between 1 and 2% in 60 min. This indicated the presence of some excipient(s) in 0·2-mg pink tablets of manufacturer A, which had an adverse effect on the stability of levothyroxine sodium. The same was not true for levothyroxine tablets of lots 4A (0·3 mg green tablets of manufacturer A) and 1B (0·2-mg pink tablets of manufacturer B).

Effect of light

When the samples of lots 1A–3A were filtered in amber-coloured vials, the decomposition of levothyroxine had decreased significantly (loss of about 2% in

60 min). This indicated that light is necessary for the excipient(s) to act as a catalyst to hasten the process of decomposition.

It is interesting to point out that manufacturer A used different kinds of bottles/lids for lot 1A versus lot 3A tablets (0·2 pink tablets). Whenever new bottles/lids are used, Good Manufacturing Practice (GMP) requires another compatibility/stability study to assure the quality of the product. The FDA also requires an ongoing stability studies programme on all dosage forms, especially those that are very susceptible to degradation such as levothyroxine sodium.

Levothyroxine sodium tablets are usually dispensed for 100 days at a time. Based on the above observations, the authors feel that lot 1A–3A (0·2-mg pink tablets of manufacturer A) may not remain stable for 100 days because tablets are exposed to light and moisture in the hands of the patients during every day use.

CONCLUSION

Levothyroxine sodium tablets (0·2 mg) from one manufacturer indicated the presence of excipient(s), which had an adverse effect on the stability of the assay sample. When compared with another lot from the same manufacturer, the new lot had an additional unidentified peak in the chromatogram. Different types of bottles/lids were used to market the same product, which is contrary to guides on good manufacturing practice unless new compatibility/stability studies are conducted. It is questionable whether those tablets can be dispensed for 100 days at a time, a common practice in pharmacies.

REFERENCES

1. **Richheimer, S.L. & Amer, T.M.** (1983) Stability-indicating assay, dissolution and content uniformity of sodium levothyroxine in tablets. *Journal of Pharmaceutical Sciences* **72**(11), 1349–1351.
2. **Brower, J.F., Tolier, D.Y. & Reepmeyer, J.C.** (1984) Determination of sodium levothyroxine in bulk, tablet and injection formulations by high-performance liquid chromatography. *Journal of Pharmaceutical Sciences* **73**(9), 1315–1317.
3. **Anonymous** (1988) *Report by the Bioequivalence Task Force* p. 45, Food and Drugs Administration, Rockville, MD, U.S.A.
4. **Anonymous** (1990) *The U.S. Pharmacopeia, 22nd Review and National Formulary, 17th Review*, pp. 765–766, The U.S. Pharmacopeial Convention, Rockville, MD, U.S.A.